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Title: Steroid-induced mental disorders in cancer patients: A systematic review

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Abstract

Corticosteroids are a central part of many cancer treatment regimens. Neuropsychiatric toxicity has complicated their use, including an association with a spectrum of symptoms, from insomnia, cognitive impairment, mood symptoms to severe mental disorders, including mania, psychosis and severe depression. Although steroid-induced mental disorders were first reported in medicine more than 60 years ago, there is a dearth of evidence available to date on optimal treatment and prevention to guide cancer clinicians. We completed a systematic review of the current evidence for therapeutic and prophylactic intervention of steroid-induced mental disorders in cancer. We searched Medline, Embase, and PsycINFO and selected studies related to steroid-induced mental disorder. The studies found were limited to case series and case reports only.

Structured Abstract

Corticosteroids are a central part of many cancer treatment regimens. Although steroid-induced mental disorders were first reported in medicine more than 60 years ago, there is a dearth of evidence available to date on optimal treatment and prevention to guide cancer clinicians. **Aim:** We completed a systematic review of the evidence for therapeutic and prophylactic interventions of steroid-induced mental disorders in cancer patients. **Methods:** We searched Medline, Embase, and PsycINFO and selected studies related to steroid-induced mental disorders. **Results:** We retrieved nineteen articles from 4025 potential articles which mainly consisted of case reports. **Conclusions:** We emphasise the limited evidence available to date and reinforce the need for well-controlled trials to guide oncology clinicians in the treatment of steroid-induced mental disorders.

Keywords: steroid-induced mental disorder, neuropsychiatric adverse effects, psychiatric disorder, corticosteroids, glucocorticoids, prednisolone, dexamethasone, mania, hypomania, psychosis

Introduction

Systemic corticosteroids are commonly prescribed for a broad range of medical conditions including immune/inflammatory disease (eg systemic lupus erythematosus (SLE) and the vasculitides), allergic conditions (eg asthma, hypersensitivity reactions, dermatitis) as well as different types of cancer. Corticosteroids are central to many cancer treatment regimens. They are used specifically in cancer to reduce inflammation, reduce tumour size, stimulate appetite, treat pain and emesis, and to prevent hypersensitivity reactions to chemotherapy [1].

Physical side-effects associated with corticosteroid treatment are also broad, and include endocrine and metabolic disturbances, fluid and electrolyte imbalances, musculoskeletal and dermatological problems and immunosuppression [2]. Systemic corticosteroids penetrate the brain and corticosteroid receptors are present in abundance in the limbic system providing a potential mechanism for neuropsychiatric effects [3].The spectrum of neuropsychiatric adverse effects attributed to systemic corticosteroids is wide-ranging and includes symptoms of anxiety, depressed mood, sleep disturbance, suicidal ideation, impaired memory and concentration as well as mental disorders including mania, psychosis, severe depression and delirium [4-8]. The Diagnostic and statistical manual of mental disorders, 5th Edition (DSM-V) lists a number of criteria for medication-induced bipolar and related disorders including significant distress and impairment in functioning [9].

Corticosteroid treatment therefore constitutes a 'double-edged sword', as one study put it, providing effective symptom relief but also problematic side-effects [8]. In cancer, neuropsychiatric effects of steroids may compromise treatment adherence and co-morbid mental disorder in cancer has a negative impact on outcome [10, 11].

When cortisone was first marketed commercially in 1950 [4], a number of troubling psychiatric side-effects were observed ranging in severity from insomnia and hypomania to psychosis and cognitive impairment [12-14]. Although the pathogenesis of these neuropsychiatric effects was poorly understood, early reports and investigations into the matter suggest that they occurred independently of a previous psychiatric history [15, 16] and that women were more likely to experience such side-effects [17, 18].

From 1966, by using standardised in-hospital monitoring, the *Boston Collaborative Drug Surveillance Program* began to quantify on a large scale the adverse effects of prescription drugs including steroids. This program was the first to report a dose-response correlation between exogenous corticosteroids and likelihood of psychiatric adverse effects among general hospital inpatients [19]. In that study of 676 general hospital inpatients, the rate of 'severe psychiatric disturbance' in those exposed to >80mg prednisone per day was 18.4%, compared with 4.6% of those receiving 40-80mg per day and 1.3% of those receiving less than 40mg per day.

Early published case series supported the Boston program findings with a 5.7% average incidence of psychiatric symptoms secondary to corticosteroid treatment [20, 21] and more recent epidemiological research supports the association between higher dose of steroid and risk of severe neuropsychiatric outcomes [22]. Other than the prescribed dose of corticosteroid, no other risk factors for steroid-induced neuropsychiatric symptoms apart from past psychiatric history, have emerged [22, 23]. While smaller early studies did not support past psychiatric history as a risk factor for steroid-induced mental disorder [7, 15, 16], more recent large-scale epidemiologic research does [22].

The clinical features of steroid side-effects have been better delineated through published case reports and case series. Symptoms such as mood or cognitive changes typically appear within three to five days of beginning steroid treatment but can also manifest during withdrawal or indeed following complete cessation of treatment [24]. Various biological mechanisms have been suggested as responsible for the observed affective and cognitive changes following systemic steroids including: an imbalance of mineralocorticoid and glucocorticoid receptors in the brain; effects of steroids on dopaminergic and cholinergic pathways and pathological effects of steroids on hippocampal neurons [23, 25, 26].

Although there are numerous published case reports and reviews on the subject of steroid-induced neuropsychiatric disorder, the majority of the articles focused in non-cancer population. The current literature appears to be limited with regard to evidence of acute and prophylactic treatment for steroid-induced disorders especially in cancer populations.

Aims and Objectives

The aim of this study was to examine the current strength of evidence for treatment and prevention of steroid-induced neuropsychiatric effects in cancer. We conducted a comprehensive systematic review of the existing literature in both adult and paediatric cancer populations to identify all evidence relating to neuropsychiatric effects of steroids, its treatment and prevention.

Methods

Search Strategy

We searched the electronic databases including Embase, MEDLINE, PsycINFO and the Cochrane Library Database between 21.04.2016 to 21.05.2016 (Appendix 1 shows the systematic review protocol). We searched all terms related to steroid, corticosteroid, glucocorticoid, prednisolone, dexamethasone and all terms related to neuropsychiatric symptoms such as mania, depression, psychosis (Appendix 2 shows the search activity). The search was limited to English language publications only. No publication date or age restrictions were imposed. A full internet search was conducted using Google and Google Scholar, and we also searched the reference lists of relevant papers.

Study selection

We screened the abstracts of the articles and retrieved the full text of relevant studies that fulfilled our inclusion criteria. Two of us (MFI and CL) selected the studies. We included studies in cancer populations only. We included studies such as observational studies, case-controlled and randomised controlled trials and case series. Only exogenous steroids including prednisolone, methylprednisolone, prednisone, dexamethasone, beclomethasone in any preparations or mode of administration were included. We excluded studies that met our exclusion criteria or had insufficient data.

Study selection and abstraction

Two authors (MFI and CL) extracted the data independently using a standardized data extraction form. The extracted data was compared and in case of disagreements between the review authors (MFI and CL), there was a consultation with a third party (EMC). The study details that were recorded include general demographic data, sample size, inclusion and exclusion criteria, dosage of steroid administered, symptom presentation and interventions given. Outcome measures reported by each study were recorded.

Data synthesis

Studies were grouped according to type of publication (ie case report, case series, other). Narrative synthesis was adopted in this study due to the limitation in type of study available.

Results

From 4025 potentially relevant citations identified, we retrieved 31 articles of which 6 were excluded (figure 1). Two of those excluded were not obtainable [27, 28]; three contained insufficient information [29-31] and one related to psychiatric adverse effects of endogenous steroid [32]. Nineteen articles [33-51] consisted of case reports; one [52] case series; two [53, 54] observational studies, one was a qualitative study [55] and two articles [56, 57] were prospective studies.

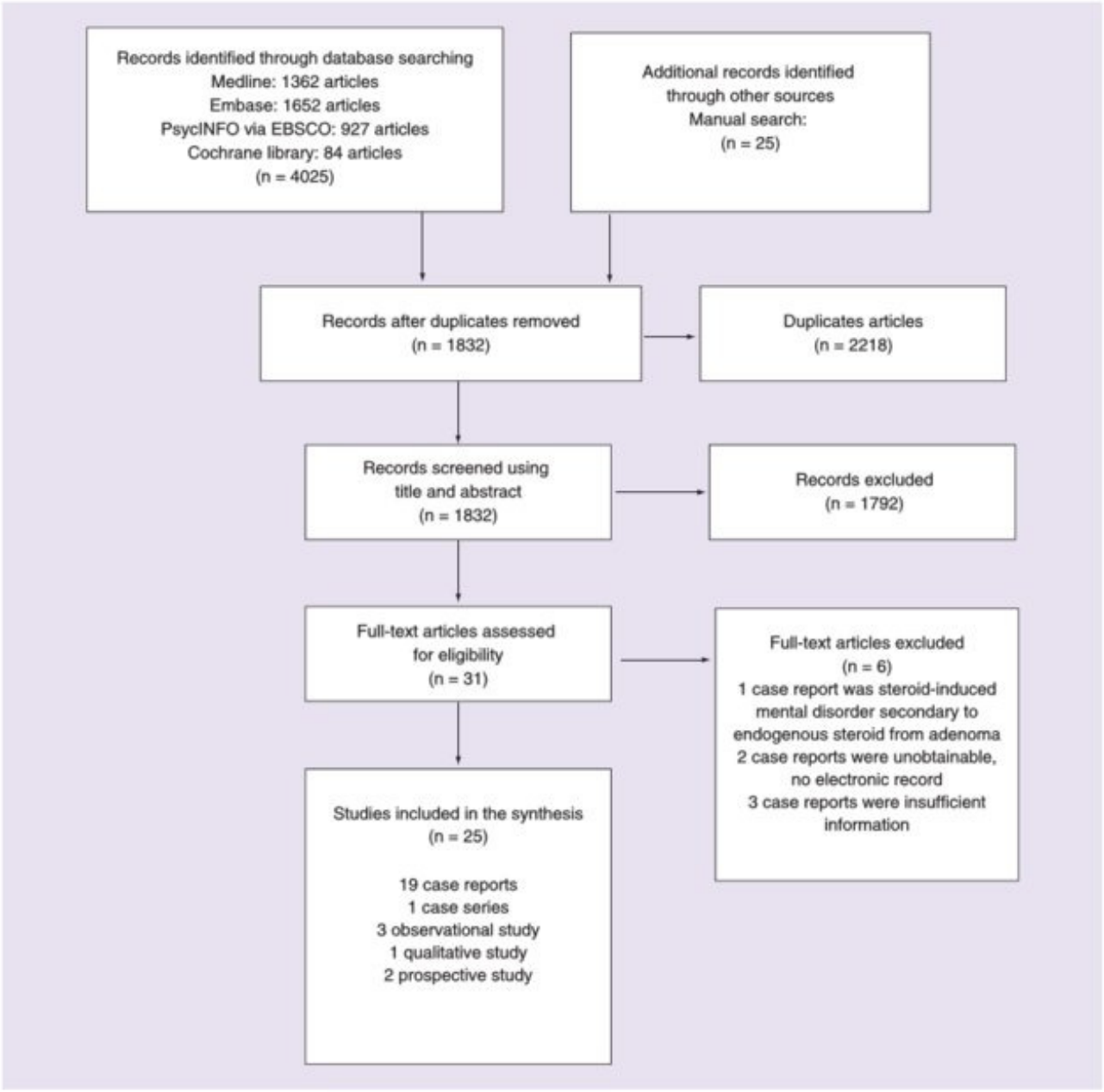

Figure 1. Flowchart of literature selection on systematic reviews of steroid-induced mental disorders in cancer patients.

Case reports

19 case reports yielded 27 cases in total (table 1). Ages ranged from 2 to 93 years old. 16 cases were less than 18 year olds. 18 out of 27 were male. Most common cancer diagnosis was acute lymphoid leukaemia (n=15), followed by lymphoma (n=4) and myeloma (n=2). Dexamethasone was the most commonly prescribed corticosteroid (n=14) followed by prednisone (n=6). Prednisone equivalent dose ranged from 16.67mg to 160mg. Fifteen out of eighteen cases with documented daily prednisone equivalent doses were over 50mg. 18 cases were treated with steroids continuously while 7 were given as pulsed therapy.

Time to onset of neuropsychiatric symptoms ranged from 1 to 30 days from the date of commencement of the steroids (Appendix 3). The most common clinical presentations were agitation (n=13), insomnia (n=9) and elation (n=8). 1 case tragically culminated in an act of homicide [33]. The most common psychiatric outcomes were manic episode (n=16) and depressive episode (n=6) (table 2). 15 cases presented with psychotic features including paranoid ideation, grandiose ideation, auditory and visual hallucination. Of those 15 cases, 2 cases were labelled as acute psychotic episodes but the case illustration does not elaborate on mood symptoms [33, 38].

Focusing on the acute intervention for steroid-induced mental disorder, of the 27 cases, 3 paediatric cases adopted a watchful waiting approach despite remaining on steroids [38]. Spontaneous symptom resolution occurred between 3 to 21 days. In one case, intervention was in the form of dividing the dose of prednisolone to four times a day [35]; in another, the intervention was to switch the steroid from oral to intravenous prednisone [47]. 6 out of 27 cases discontinued the steroid as part of the acute intervention. 21 cases required psychotropic medication for acute intervention. The most common psychotropic medication used was risperidone (n=8). 7 of these cases were paediatric. Other psychotropic medications used were benzodiazepine only (n=2), promethazine (n=1), antidepressants (n=4) including citalopram, imipramine, paroxetine, mianserin and sertraline, and other antipsychotic medications including haloperidol (n=4), olanzapine (n=2), aripiprazole (n=1), loxepine (n=1) and quetiapine (n=1). Only 1 case used the mood stabiliser lithium carbonate and in that case Lithium was used concurrently with antipsychotic medication [50].

Time to improvement or full resolution of symptoms in the case reports varied. The range for improvement of symptoms was between 1 and 21 days. The majority of the cases improved within seven days. 18 cases were followed up following re-exposure to steroid. 10 cases had a recurrence of mental disorder following the introduction of steroids [37-41, 48, 49]. With regard to prophylactic strategies to prevent recurrence, two out of eight cases without recurrence adopted a divided steroid strategy [35], three cases continued on antipsychotic and mood stabiliser following the first acute presentation [41, 43, 50], and in another case the steroid was removed from the chemotherapy regimen [46]. Seven cases adopted a targeted approach using psychotropic medication during the course of steroids [37-40, 48, 49].

Case series

One case series of 20 patients with steroid-induced mania were treated with sodium valproate, five of whom were oncology patients: four had multiple myeloma and one had metastatic breast cancer [52]. Patients were recruited from consecutive in-patient referrals to a consultation-liaison psychiatry service over a six-year period. Patients who developed steroid-induced mania following steroid treatment were included in this study. Sodium valproate 500 mg twice daily was administered to all patients and dosage was modified according to the valproate level on day three. Patients were followed up daily and Young Mania Rating Scale (YMRS) was used daily to monitor the severity of manic symptoms over a four-day period. The study shows a rapid improvement of manic symptoms within 48 hours with complete resolution in 72 hours.

Other studies

One study [56] evaluated the incidence of steroid-induced neuropsychiatric episodes in adolescents with acute lymphocytic leukaemia (ALL). Of 37 patients included, one third of the patients showed mild behavioural disturbances. The most common symptoms were anxiety, mood lability and depressive symptoms. 4 adolescents (11%) developed acute neuropsychiatric episodes which included severe anxiety, auditory and visual hallucinations and impairment in level of consciousness following the reduction of steroids. In the study, two patients were treated with antidepressants and the remaining ten patients with symptoms of behaviour disturbances were treated with antihistamine (hydroxyzine).

Another study [53] was a retrospective chart review of patients who were referred to a psycho-oncology liaison service. The study examined clinical symptoms and levels of subjective distress in cancer patients who were treated with steroids. These patients were compared to cancer patients who did not receive steroids. The study showed that the steroid group was associated with a higher likelihood of presenting with poor concentration, psychomotor agitation, elevated mood, irritability and behavioural changes compared to the non-steroid group.

One study was a qualitative study evaluating the psychological and psychiatric sequelae of steroids in haematological patients [55]. This study provided evidence that emotional disturbances were associated with corticosteroid use in patients with haematological cancers. Importantly, such disturbances were shown to be independent of the individual's underlying emotional health.

Two studies focused on insomnia in oncology patients receiving corticosteroids [54, 57]. One retrospective cohort study of patients with recurrent glioma showed that insomnia was associated with the use of dexamethasone and anti-epileptic medication [54]. Another study was a prospective case-control study which showed that oncology patients who received high-dose glucocorticoids as part of their chemotherapy developed insomnia. The use of hypnotics did not significantly improve the quality of their sleep [57].

Discussion

Summary of main results

In this comprehensive systematic review, we were unable to find any clinical trials relating to the acute treatment or prophylaxis of steroid-induced mental disturbances in cancer populations. Strategies to treat steroid-induced mental disorders included adjusting/discontinuing the steroid preparation, or administering psychotropic medications (most commonly antipsychotics) followed by the mood stabilizers such as lithium, sodium valproate, benzodiazepines or antidepressants. Two strategies were observed in the case reports relating to the prevention of recurrence. The first strategy involved continuation of psychotropic medication following the first episode; the second strategy involved a targeted approach in which the antipsychotic medication or mood stabiliser was introduced several days before, or on the day of, steroid commencement.

In non-cancer populations, only two studies to our knowledge (using the same search methodology as per cancer populations) have focused on acute treatment and prophylaxis [58, 59] of steroid-induced mental disorders. The first study examined the use of lithium as a prophylactic agent in the management of steroid-induced psychiatric side-effects in 27 patients with multiple sclerosis or retro-bulbar neuritis [58]. None of the patients who were administered lithium pre-treatment developed psychiatric side effects whilst on corticosteroid therapy. Conversely, 14% of a historical comparison group of 44 patients who were not pre-treated with lithium became psychiatrically unwell. The study concluded that lithium prophylaxis might prevent steroid-induced psychosis and other psychiatric symptoms; however, it emphasised that further controlled prospective studies were needed to corroborate this finding. The second study, an open-label trial of olanzapine for corticosteroid-induced mood symptoms examined the use of olanzapine in 12 outpatients with manic or mixed affective symptoms secondary to corticosteroid treatment [59]. Using well-validated rating scales, the study showed that olanzapine improved mood in treated subjects and appeared to be well tolerated.

Steroid effects in cancer patients

The exact prevalence of steroid-induced neuropsychiatric effects in cancer patients is unknown. The Boston Collaborative Drug Surveillance Programme first reported the incidence of steroid-induced psychiatric symptoms in the context of a dose-response correlation. Symptoms were noted in 1.3% of 463 patients on prednisolone 40 mg daily, 4.6% of 175 patients on 41-80 mg daily, and 18.4% of 38 patients on 80 mg or more daily [15]. Since then, studies in cancer patients in particular have shown a 5-10% incidence of neuropsychiatric effects in patients on high doses of steroids. Mania and hypomania are the most common steroid-induced psychiatric effects in non-cancer patients [18], and there is a suggestion that depression can occur in cases of chronic steroid use [55].

The neuropsychiatric effects of corticosteroids in cancer patients can occur very early on during the treatment programs; however, it may not be diagnosed early. This can adversely

affect patient outcomes by further delaying cancer treatments. Evidence-based guidelines are needed on how best to prevent and treat neuropsychiatric steroid effects. However, the relative paucity of large-scale, robust, placebo-controlled studies in this field has meant that prevention and treatment are largely based on anecdotal evidence.

Although there are numerous published case reports and reviews on the subject of steroid-induced neuropsychiatric disorder, evidence-based literature related to both prevention and treatment of this common problem appears to be limited, particularly in cancer patients. Corticosteroids are a key part of chemotherapy for certain types of cancer such as haematological cancer. They are also used post-operatively, particularly in head and neck cancers. As corticosteroids improve survival rates in cancer patients, their use in cancer treatment regimens is paramount. However, it is equally significant that cancer patients are at an increased risk of suicide compared to the cancer-free population [60-62], and corticosteroids are shown to increase the risk of suicidality in a small study of a non-cancer population [16]. Therefore, the use of steroids in this particular cohort of patients ought to be judicious.

The only available evidence to date is based on open-label trials, cohort studies, and case series in non-cancer patients. Studies on cancer patients receiving corticosteroid treatment regimens have shown that organic mood disorders and delirium are the most frequently encountered neuropsychiatric problems [17]. Further studies with cancer patients are needed wherein important variables including past psychiatric history, type and site of cancer, neurological complications secondary to the malignant process, and general physical health are controlled [17]. It is important to add that steroid-related cognitive and mood changes can be difficult to diagnose in cancer patients by virtue of the fact that cancer is a multisystem disease [32]. Therefore, such changes in the mental state need to have their exact aetiology refined and delineated [17]. This issue also extends to the paediatric cancer cohort where steroids may form an integral part of treatment for acute lymphoblastic leukaemia and Hodgkin's lymphoma [7].

Strengths of the study

To the best of our knowledge, this is the first systematic review of steroid-induced neuropsychiatric effects in cancer patients that provides a comprehensive overview of the available evidence on prevention and treatment of these effects and the challenges they pose to clinicians. Search terms employed to source relevant articles were sensitive, capturing a broad range of symptoms and diagnoses relevant to steroid-induced mood disorders.

Limitations of the study

We excluded non-English articles and therefore may have missed some published cases. Further, although our search strategy was comprehensive, it may not have captured all the relevant articles available, as some may have utilised terminology other than that employed in our literature search.

Implications for practice

Oncology is a discipline in which clinical trials are a key part of everyday practice. There is a clear need for clinical trials to enhance the evidence base for the prevention and treatment of steroid-induced mental disorders in cancer. These mental disorders are not rare and have a significant morbidity. Evidence-based clinical guidelines on the management of steroid-induced neuropsychiatric effects are lacking both in the existing literature and in practice. Such guidelines or recommendations need to be established. To date, no such guidelines or recommendations have been established, resulting in heavy reliance on anecdotal evidence for the management of these effects.

With respect to options for clinical management, evidence suggests that steroid dose reduction or weaning is a favoured strategy in cases of severe mental and behavioural disturbance, as is a watchful waiting approach in milder cases. Another treatment strategy is to employ evidence-based guidelines for the management of overt hypomania, mania or psychosis. This involves treating steroid-induced neuropsychiatric effects with antipsychotic medication and a mood stabiliser such as lithium or sodium valproate if no improvement is noted. Psychoeducation plays an important role in the management of these effects; patients treated with corticosteroids ought to be advised specifically about the possible range of neuropsychiatric symptoms secondary to steroid use.

Implications for research

There is a clear gap in research on the subject of prevention and treatment of steroid-induced mental disorders. Additional randomised controlled trials are needed to examine preventive strategies, such as the prophylactic use of psychotropic medication in patients who experience steroid-induced mental disorders. It would be useful to assess the impact of steroid-induced mood disorders and potential treatments in cancer populations in particular. This involves a number of questions for future research, such as if steroid-induced mental disorders delay cancer interventions or affect compliance with cancer treatment regimens, if cancer treatments in oncology patients with steroid-induced neuropsychiatric effects adversely affect health outcomes, and if patient survival is affected as a consequence of these.

Conclusion

The range of neuropsychiatric side effects of corticosteroid treatment is broad, varying from mild mood changes to mania and psychosis. There is a paucity of robust clinical research on the prevention and treatment of these effects, particularly in relation to cancer patients. This study has demonstrated that various strategies can be employed to treat mental and behavioural disturbances secondary to the administration of steroids, as well as prevent their recurrence, both in cancer and non-cancer patients. However, it also emphasises the limited evidence for these treatment and prevention strategies, which are needed to guide clinicians in the prevention and treatment of steroid-induced psychiatric disorders. This research gap should be addressed as a priority through multi-centre clinical trials.

Future Perspectives

There is a clear gap in research on the subject of prevention and treatment of steroid-induced mental disorders. We speculate that at the initial stage, researchers will focus on the impact of steroid-induced mood disorders to address a number of questions, such as if steroid-induced mental disorders delay cancer interventions or affect compliance with cancer treatment regimens, which may affect morbidity and mortality.

In the future, more research will be conducted to assess the predictive factors and the risk of developing steroid-induced mental disorders following corticosteroid treatment. Furthermore, this will lead to a development of screening tools to stratify the risk and guide clinicians with regard to treatment and prophylaxis.

We also envision that in the future there will exist an established guideline for the acute treatment of, and guidelines in the management of the recurrence of, steroid-induced mental disorders. Antipsychotic medication and mood stabilisers will most likely provide the mainstay of treatment for steroid-induced mood disorders.

Table 1. Summary of case reports

Author (year)	Age	Sex	Cancer diagnosis	Corticosteroids	Average daily dose	Prednisone equivalent daily dose	Days of onset	Clinical Presentations
Glynne-Jones (1986)	19	f	Hodgkin's lymphoma	Prednisone	40mg/day - continuous	40mg	-	Agitation, insomnia, anxiety, paranoid ideation
Glynne-Jones (1986)	56	m	Hodgkin's lymphoma	Prednisone	90mg/day- continuous	90mg	-	Elation, obsessional, overactive
Grigg (1989)	62	f	Multiple myeloma	Prednisone	60mg/day - continuous therapy	60mg	13	Agitation, elation, followed by depressive symptoms and catatonia
Watanabe (1994)	17	f	ALL	Dexamethasone	15mg/day - continuous therapy	100mg	14	Agitation, insomnia, elation, disinhibition
Watanabe (1994)	13	f	ALL	Dexamethasone	15mg/day - continuous therapy	100mg	14	Insomnia, anxiety, panic attacks
Kramer (1999)	14	f	Pre-B-cell ALL	Dexamethasone	24mg/day - continuous therapy	160mg	25	Agitation, visual hallucination, religious delusion, formication
Jenkins (2000)	53	f	Meningioma	Dexamethasone	16mg/day - continuous therapy	106.67mg	1	Agitation, depressive symptoms, visual and auditory hallucination, suicide attempt
Jenkins (2000)	93	m	Renal cell carcinoma	Dexamethasone	20mg/day - continuous therapy	133.33mg	4	Agitation, insomnia, cognitive impairment, visual hallucination
Ingram (2003)	2	m	ALL - GVHD	Methylprednisolone	2mg/kg then 4mg/kg - continuous therapy	-	1	Agitation, irritability, pressured speech, visual hallucination, self-injurious behaviour
Ito (2003)	37	f	AML - GVHD	Prednisolone	50mg/day - continuous therapy	50mg	4	Agitation, anxiety, depressive symptoms, suicidal ideation
Hochhauser (2005)	4	m	ALL	Unspecified	Unspecified dose - pulses therapy	-	14	Agitation, aggressive outburst, irritability
Hochhauser (2005)	4	m	ALL	Dexamethasone	Unspecified dose - pulses therapy	-	6	Aggressive outburst, irritability, behavioural difficulties and bizarre behaviours disturbance, bizarre behaviour
Hochhauser (2005)	15	m	B-Cell lymphoma	Dexamethasone	Unspecified dose	-	7	Mood-lability, physical and verbal aggression.
Hochhauser (2005)	6	m	ALL	Unspecified	Unspecified dose - pulses therapy	-	4	Mood-lability, aggressive behaviours, paranoid ideation
Mercadante (2007)	48	m	IgG Myeloma	Dexamethasone	8mg/day - continuous therapy	53.33mg	21	Mood-lability, irritability, dysphoria, pressured speech, disinhibition
Mian (2007)	14	m	Hodgkin's lymphoma	Prednisone	75mg/day - pulse therapy	75mg	15	Agitation, elation, grandiose delusion, pressured speech, visual hallucination
Joshi (2008)	4	f	ALL	Dexamethasone	6mg/m2 - continuous therapy	40mg	-	Irritability, emotional outburst
Okishiro (2009)	67	m	Mesothelioma	Betamethasone	2mg/day - continuous therapy	16.67mg	3	Bizarre behaviours, change in personality, disorientation, blunted affect
Tutkunkardas (2010)	14	m	T-cell ALL	Dexamethasone	Unspecified dose - pulses therapy	-	5	Mood-lability, irritability, anger outburst, suicidal ideation
Ularntinon (2010)	8	m	T-cell ALL	Prednisone	2mg/kg - continuous therapy	-	12	Elation, grandiose ideation, prophetic delusion, insomnia
Ularntinon (2010)	16	m	Pre-B-cell ALL	Dexamethasone	12mg - 5 day pulses therapy	80mg	-	Agitation, irritability, and thoughts of harming others
Ularntinon (2010)	10	m	Pre-B-cell ALL	Dexamethasone	0.25mg/kg - 5 day pulses therapy	-	-	Insomnia, elation, pressured speech, grandiose delusion
Airagnes (2011)	77	m	CLL	Methylprednisolone	80mg - continuous therapy	100mg	22	Insomnia, elation, paranoid psychosis, homicide
Cassidy (2012)	17	m	ALL	Dexamethasone	10mg - continuous therapy	66.67mg	28	Insomnia, elation, grandiose delusion
Kimmel (2012)	55	f	Metastatic breast cancer	Dexamethasone	8mg/day - continuous therapy	53.33mg	28	Agitation, insomnia, irritability, thought disorder
Hechtman (2013)	14	m	ALL	Prednisone	Unspecified	-	14	Agitation, auditory and visual hallucination, pressured speech
Zincir (2014)	29	m	ALL	Dexamethasone	20mg - continuous therapy	133.33mg	30	Depressive symptoms, lost appetite, passive death wish and suicide attempt

ALL = Acute lymphocytic leukaemia, GVHD = Graft-versus-host disease, AML = Acute myeloid leukaemia, IgG = Immunoglobulins G

Table 2. Summary of diagnostic outcome and intervention

Author (year)	Age	Sex	Cancer diagnosis	Psychiatric diagnosis	Acute intervention	Time to improvement	Recurrence	Strategy to prevent recurrence
Glynne-Jones (1986)	19	f	Hodgkin's lymphoma	Manic episode with psychosis	Steroid was given in divided dose 10mg four times daily	-	No	Steroid given in divided dose
Glynne-Jones (1986)	56	m	Hodgkin's lymphoma	Manic episode	Steroid was tapered down to 10mg	14 days	No	Steroid given in divided dose
Grigg (1989)	62	f	Multiple myeloma	Severe depressive disorder	Steroid was stopped, haloperidol 2mg single dose	2 days	-	
Watanabe (1994)	17	f	ALL	Manic episode	Haloperidol 10mg/day, lithium carbonate 900mg/day	7 days	No	Lithium was continued as maintenance treatment while on steroid
Watanabe (1994)	13	f	ALL	Anxiety disorder	Imipramine 100mg/day	7 days	No	Imipramine was continued while on steroid
Kramer (1999)	14	f	Pre-B-cell ALL	Manic episode with psychosis	Steroid was stopped, lorazepam initially, then risperidone 4mg/day	3 days	-	
Jenkins (2000)	53	f	Meningioma	Agitated psychotic depression	Steroid was discontinued, Risperidone, lorazepam, paroxetine	14 days	Yes	Haloperidol daily, paroxetine and lorazepam
Jenkins (2000)	93	m	Renal cell carcinoma	Mixed delirium and mania	Steroid was reduced, haloperidol	14 days	No	
Ingram (2003)	2	m	ALL - GVHD	Manic episode with psychosis	Steroid was continued, promethazine 0.5mg/kg four times daily	2 hours	Yes	Targeted approach - promethazine 0.5mg/kg given up to 4 times a day
Ito (2003)	37	f	AML - GVHD	Severe depressive disorder	Mianserin 40mg - no effects, lithium carbonate 300mg/day added	4 days	Yes	Targeted approach - lithium carbonate 200mg/day
Hochhauser (2005)	4	m	ALL	Steroid-induced mood disturbance	Watch and wait	2 days	Yes	
Hochhauser (2005)	4	m	ALL	Acute psychotic episode	Lorazepam 0.5mg PRN	2 days	Yes	Targeted approach - chlorpromazine during steroids
Hochhauser (2005)	15	m	B-Cell lymphoma	Manic episode	Watch and wait	7 days	Yes	Switch to prednisone - no effects, trial of escitalopram 5mg with no effects.
Hochhauser (2005)	6	m	ALL	Manic episode with psychosis	Watch and wait	21 days	-	
Mercadante (2007)	48	m	IgG Myeloma	Manic episode	Steroid was re-introduced 4mg/day, continuous IV midazolam 22mg/day	3 days	-	
Mian (2007)	14	m	Hodgkin's lymphoma	Manic episode with psychosis	Steroid was stopped, Olanzapine initially, switched to haloperidol in acute phase then switched to quetiapine	7 days	No	Steroid was removed from the chemotherapy regimes
Joshi (2008)	4	f	ALL	Depressive disorder	Steroid was continued, citalopram 2.5mg/day added	28 days	No	
Okishiro (2009)	67	m	Mesothelioma	Severe depressive episode with psychotic features	Switched to intravenous prednisolone (10mg/day)	7 days	-	
Tutkunkardas (2010)	14	m	T-cell ALL	Manic episode with psychosis	Steroid continued. Risperidone 0.5mg	2 days	Yes	Targeted approach - Risperidone 0.5mg when receive steroid
Ularntinon (2010)	8	m	T-cell ALL	Manic episode with psychosis	Steroid continued. Risperidone 1.5mg	3 days	Yes	Targeted approach - Risperidone 1.5mg at start until 7 days post steroid cessation
Ularntinon (2010)	16	m	Pre-B-cell ALL	Manic episode with psychosis	Steroid continued. Risperidone 0.5mg	1 day	Yes	Targeted approach - Risperidone 0.5mg
Ularntinon (2010)	10	m	Pre-B-cell ALL	Manic episode	Steroid was continued, Risperidone 3mg-5mg/day	14 days	-	
Airagnes (2011)	77	m	CLL	Acute psychotic episode	Steroid was stopped. Loxepine 100mg/day	3 days	-	
Cassidy (2012)	17	m	ALL	Manic episode with psychosis	Risperidone 3mg. Lorazepam 0.5mg prn, steroid continued	21 days	-	
Kimmel (2012)	55	f	Metastatic breast cancer	Manic episode	Steroid was stopped, Olanzapine 5mg, switched to aripiprazole 10mg and clonazepam 1mg/day	3 days	No	Aripiprazole was continued up to 5 weeks after steroid was discontinued
Hechtman (2013)	14	m	ALL	Manic episode with psychosis	Steroid continued, Risperidone 1mg, stimulant stopped	21 days	Yes	Targeted approach - Risperidone 1mg day before steroid and reduce at day two after steroid discontinued
Zincir (2014)	29	m	ALL	Severe depressive episode with psychotic features	Steroid stopped. Olanzapine 10mg, Sertraline 50mg, ECT 7 sessions	-	-	

ALL = Acute lymphocytic leukaemia, GVHD = Graft-versus-host disease, AML = Acute myeloid leukaemia, IgG = Immunoglobulins G, ECT = electroconvulsive therapy

Executive Summary

- Corticosteroids are central to many cancer treatment regimens. However, corticosteroids can lead to serious neuropsychiatric adverse effects including mania, psychosis, severe depression and deslirium.
- Although there are numerous published case reports and reviews on the subject of steroid-induced neuropsychiatric disorder, the majority of the articles focused on non-cancer populations.
- In this systematic review, we were unable to find any clinical trials relating to the acute treatment or prophylaxis of steroid-induced mental disturbances in cancer populations. The results were limited to case reports and case series.
- Strategies to treat steroid-induced mental disorders included adjusting/discontinuing the steroid preparation, or administering psychotropic medications (most commonly antipsychotics) followed by mood stabilizers such as lithium, sodium valproate, benzodiazepines or antidepressants.
- Two strategies were observed in the case reports relating to the prevention of recurrence. The first strategy involved continuous use of psychotropic medication following the first episode; the second strategy involved a targeted approach.
- There is a clear gap in research on the subject of prevention and treatment of steroid-induced mental disorders. Additional randomised controlled trials are needed to examine treatment strategies in the acute and prophylactic treatment of steroid-induced mental disorder

References

1. Wooldridge JE, Anderson CM, Perry MC. Corticosteroids in advanced cancer. *Oncology (Williston Park)* 15(2), 225-234; discussion 234-226 (2001).
2. Stanbury RM, Graham EM. Systemic corticosteroid therapy--side effects and their management. *Br J Ophthalmol* 82(6), 704-708 (1998).
3. Mcewen BS, Gray JD, Nasca C. Redefining neuroendocrinology: stress, sex and cognitive and emotional regulation. *The Journal of endocrinology* 226(2), T67-83 (2015).
4. Rome HP, Braceland FJ. Psychological response to corticotropin, cortisone, and related steroid substances. Psychotic reaction types. *Journal of the American Medical Association* 148 27-30 (1952).
5. Brown ES, Chandler PA. Mood and Cognitive Changes During Systemic Corticosteroid Therapy. *Prim Care Companion J Clin Psychiatry* 3(1), 17-21 (2001).
6. Sirois F. Steroid psychosis: A review. *General Hospital Psychiatry* 25(1), 27-33 (2003).
7. Warrington TP, Bostwick JM. Psychiatric adverse effects of corticosteroids. *Mayo Clinic Proceedings* 81(10), 1361-1367 (2006).
8. Drozdowicz LB, Bostwick JM. Psychiatric adverse effects of pediatric corticosteroid use. *Mayo Clinic Proceedings* 89(6), 817-834 (2014).
9. Bipolar and Related Disorders In: *Diagnostic and Statistical Manual of Mental Disorders (5th ed)*, (Ed.^(Eds).American Psychiatric Association Arlington, VA (2013).
10. Kisely S, Crowe E, Lawrence D. Cancer-related mortality in people with mental illness. *JAMA Psychiatry* 70(2), 209-217 (2013).
11. Ribe AR, Laurberg T, Laursen TM, Charles M, Vedsted P, Vestergaard M. Ten-Year Mortality after a Breast Cancer Diagnosis in Women with Severe Mental Illness: A Danish Population-Based Cohort Study. *PLoS One* 11(7), e0158013 (2016).
12. Clark LD, Bauer W, Cobb S. Preliminary observations on mental disturbances occurring in patients under therapy with cortisone and ACTH. *The New England journal of medicine* 246(6), 205-216 (1952).
13. Clark LD, Quarton GC, Cobb S, Bauer W. Further observations on mental disturbances associated with cortisone and ACTH therapy. *The New England journal of medicine* 249(5), 178-183 (1953).
14. Lewis A, Fleminger JJ. The psychiatric risk from corticotrophin and cortisone. *Lancet* 266(6808), 383-386 (1954).
15. Kirsner JB, Palmer WL, Spencer JA, Bicks RO, Johnson CF. Corticotropin (ACTH) and the adrenal steroids in the management of ulcerative colitis: observations in 240 patients. *Ann Intern Med* 50(4), 891-927 (1959).
16. Marx FW, Jr., Barker WF. Surgical results in patients with ulcerative colitis treated with and without corticosteroids. *Am J Surg* 113(2), 157-164 (1967).
17. Bunim JJ, Ziff M, Mc EC. Evaluation of prolonged cortisone therapy in rheumatiod arthritis: a four-year study. *The American journal of medicine* 18(1), 27-40 (1955).
18. Boye Nielsen J, Drivsholm A, Fischer F, Brochner-Mortensen K. Long-term treatment with corticosteroids in rheumatoid arthritis (over a period of 9 to 12 years). *Acta Med Scand* 173 177-183 (1963).
19. Acute adverse reactions to prednisone in relation to dosage. *Clin Pharmacol Ther* 13(5), 694-698 (1972).
20. Lewis DA, Smith RE. Steroid-induced psychiatric syndromes. A report of 14 cases and a review of the literature. *Journal of Affective Disorders* 5(4), 319-332 (1983).

21. Stiefel FC, Breitbart WS, Holland JC. Corticosteroids in cancer: Neuropsychiatric complications. *Cancer Investigation* 7(5), 479-491 (1989).
22. Fardet L, Petersen I, Nazareth I. Suicidal behavior and severe neuropsychiatric disorders following glucocorticoid therapy in primary care. *American Journal of Psychiatry* 169(5), 491-497 (2012).
23. Wolkowitz OM, Reus VI, Canick J, Levin B, Lupien S. Glucocorticoid medication, memory and steroid psychosis in medical illness. *Ann N Y Acad Sci* 823 81-96 (1997).
24. Wolkowitz O. Suicidality and corticosteroid psychosis. *Biological Psychiatry* 27(4), 459 (1990).
25. Kenna HA, Poon AW, De Los Angeles CP, Koran LM. Psychiatric complications of treatment with corticosteroids: Review with case report. *Psychiatry and Clinical Neurosciences* 65(6), 549-560 (2011).
26. Judd LL, Schettler PJ, Brown ES *et al*. Adverse consequences of glucocorticoid medication: psychological, cognitive, and behavioral effects. *Am J Psychiatry* 171(10), 1045-1051 (2014).
27. Miller LJ. Psychiatric effects of corticosteroids. *Cancer Bulletin* 43(3), 275-276 (1991).
28. Venkatarangam SH, Kutcher SP, Notkin RM. Secondary mania with steroid withdrawal. *The Canadian Journal of Psychiatry / La Revue canadienne de psychiatrie* 33(7), 631-632 (1988).
29. Brewster D, Barrat-Gordon R, Schuermeyer I. Steroid withdrawal psychosis: A case report. *Psycho-Oncology* 19 S95-S96 (2010).
30. Khosh-Chashm D, Bailey N, Parsaik A. Prevalence and treatment of subsyndromal steroid-induced mood lability, anxiety, and insomnia in cancer patients: A case series and literature review. *Psycho-Oncology* 24 190 (2015).
31. Samsel C, Loucas C, Muriel A. Treatment of steroid-induced mood disorder in co-morbid developmentally delayed youth with cancer. *Psycho-Oncology* 24 175-176 (2015).
32. Osei-Agyemang T. An atypical thymic carcinoid producing ectopic adrenocorticotropic hormone causing cushing's syndrome initially presenting with severe steroid psychosis. *Interactive Cardiovascular and Thoracic Surgery* 21 (2015).
33. Airagnes G, Rouge-Maillart C, Garre JB, Gohier B. Homicide and associated steroid acute psychosis: A case report. *Case Reports in Medicine* 2011 (2011).
34. Cassidy C, Sahay S, Mcnicholas F. Steroid-induced mania: A case report. *Irish Journal of Psychological Medicine* 29(3), 194-195 (2012).
35. Glynne-Jones R, Vernon CC, Bell G. Is steroid psychosis preventable by divided doses? *Lancet* 2(8520), 1404 (1986).
36. Grigg JR. Prednisone mood disorder with associated catatonia. *Journal of geriatric psychiatry and neurology* 2(1), 41-44 (1989).
37. Hechtman L, Russell RC, Young LJ. Psychosis in a boy with ADHD treated with stimulants and acute lymphocytic leukemia treated with chemotherapy and steroids. *Neuropsychiatry* 3(1), 17-21 (2013).
38. Hochhauser CJ, Lewis M, Kamen BA, Cole PD. Steroid-induced alterations of mood and behavior in children during treatment for acute lymphoblastic leukemia. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer* 13(12), 967-974 (2005).
39. Ingram DG, Hagemann TM. Promethazine treatment of steroid-induced psychosis in a child. *Annals of Pharmacotherapy* 37(7-8), 1036-1039 (2003).
40. Ito M, Onose M, Yamada T, Onishi H, Fujisawa S, Kanamori H. Successful lithium carbonate treatment for steroid-induced depression following bone marrow

transplantation: A case report. *Japanese Journal of Clinical Oncology* 33(10), 538-540 (2003).
41. Jenkins CA, Bruera E. Difficulties in diagnosing neuropsychiatric complications of corticosteroids in advanced cancer patients: Two case reports. *Journal of Pain and Symptom Management* 19(4), 309-317 (2000).
42. Joshi DD. Treating dexamethasone-induced mood disorders in children with leukemia. *Pediatric Blood and Cancer* 51(1), 147 (2008).
43. Kimmel RJ, Combs H. Steroid-Induced Mania Treated with Aripiprazole. *Psychosomatics* 53(2), 181-183 (2012).
44. Kramer TM, Cottingham EM. Risperidone in the treatment of steroid-induced psychosis. *Journal of Child and Adolescent Psychopharmacology* 9(4), 315-316 (1999).
45. Mercadante S, Villari P, Intravaia G. Withdrawal acute psychosis after corticosteroid discontinuation. *J Pain Symptom Manage* 34(2), 118-119 (2007).
46. Mian I, Gearing R, Desouza C, Solomon L. Corticosteroid-related psychiatric complications in the treatment of Hodgkin's lymphoma in an adolescent. *Journal of the Canadian Academy of Child and Adolescent Psychiatry* 16(1), 27-29 (2007).
47. Okishiro N, Tanimukai H, Tsuneto S, Ito N. Can "steroid switching" improve steroid-induced psychosis in a patient with advanced cancer? *Journal of Palliative Medicine* 12(5), 487-490 (2009).
48. Tutkunkardas MD, Mukaddes NM. Drug induced mania in a boy with high functioning autism. *Psychopharmacol Bull* 43(2), 82-85 (2010).
49. Ularntinon S, Tzuang D, Dahl G, Shaw RJ. Concurrent treatment of steroid-related mood and psychotic symptoms with risperidone. *Pediatrics* 125(5), e1241-e1245 (2010).
50. Watanabe TK, Sylvester CE, Manaligod JM. Mania or panic associated with dexamethasone chemotherapy in adolescents. *Journal of Adolescent Health* 15(4), 345-347 (1994).
51. Zincir S, Kartal P, Bozkurt-Zincir S. Corticosteroid induced psychotic depression: A case report. *Klinik Psikofarmakoloji Bulteni* 24 S175-S176 (2014).
52. Roxanas MG, Hunt GE. Rapid reversal of corticosteroid-induced mania with sodium valproate: A case series of 20 patients. *Psychosomatics* 53(6), 575-581 (2012).
53. Hassab Errasoul AH, Cassidy E, Bowler A. Steroid induced psychiatric disorders in cancer patients referred for Liaison psycho oncology service. *Psycho-Oncology* 19 S13 (2010).
54. Peters KB, Reardon DA, Vredenburgh JJ, Desjardins A, Friedman HS. Retrospective analysis of insomnia in recurrent glioma patients and its association with dexamethasone and anti-epileptics. *Neuro-Oncology* 12 iv104 (2010).
55. Mcgrath P, Patton MA, James S. "I was never like that": Australian findings on the psychological and psychiatric sequelae of corticosteroids in haematology treatments. *Supportive Care in Cancer* 17(4), 339-347 (2009).
56. Samardakiewicz M, Mitura-Lesiuk M, Kowalczyk JR. Corticosteroids-induced neuropsychiatric episodes in acute lymphoblastic leukemia adolescent patients. *Psycho-Oncology* 22(s3), 124-362 (2013).
57. Zhao J, Dai YH, Xi QS, Yu SY. A clinical study on insomnia in patients with cancer during chemotherapy containing high-dose glucocorticoids. *Pharmazie* 68(6), 421-427 (2013).
58. Falk WE, Mahnke MW, Poskanzer DC. Lithium prophylaxis of corticotropin-induced psychosis. *Jama* 241(10), 1011-1012 (1979).

59. Sherwood Brown E, Chamberlain W, Dhanani N, Paranjpe P, Carmody TJ, Sargeant M. An open-label trial of olanzapine for corticosteroid-induced mood symptoms. *Journal of Affective Disorders* 83(2-3), 277-281 (2004).

60. Fang F, Fall K, Mittleman MA *et al*. Suicide and cardiovascular death after a cancer diagnosis. *The New England Journal of Medicine* 366, 1310-8 (2012).

61. Yousaf U, Christensen MLM, Engholm G, Storm HH. Suicides among Danish cancer patients 1971–1999. *British Journal of Cancer* 92(6), 995-1000 (2005).

62. Camidge DR, Stockton DL, Frame S, Wood R, Bain M, Bateman DN. Hospital admissions and deaths relating to deliberate self-harm and accidents within 5 years of a cancer diagnosis: a national study in Scotland, UK. *British Journal of Cancer* 96(5), 752-757 (2007).

Reference annotations

1. Fang F, Fall K, Mittleman MA *et al*. Suicide and cardiovascular death after a cancer diagnosis. *The New England Journal of Medicine* 366, 1310-8 (2012).**

   This is the largest epidemiological study to date that estimates the relative risk of suicide following a cancer diagnosis.

2. Sherwood Brown E, Chamberlain W, Dhanani N, Paranjpe P, Carmody TJ, Sargeant M. An open-label trial of olanzapine for corticosteroid-induced mood symptoms. *Journal of Affective Disorders* 83(2-3), 277-281 (2004).**

   This is the largest study to date to focus on the acute treatment of steroid-induced mood sympmtoms with antipsychotic medication in a non-cancer population.

3. Roxanas MG, Hunt GE. Rapid reversal of corticosteroid-induced mania with sodium valproate: A case series of 20 patients. *Psychosomatics* 53(6), 575-581 (2012).*

   This is the largest case series on the use of sodium valproate as a mood stabiliser in the treatment of steroid-induced mania

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Contributions of authors

All authors (MFI, CL and EMC) contributed to the development of the review questions. MFI and CL drafted the systematic review protocol. MFI designed and implemented the searches. MFI and CL extracted the data independently. MFI and CL assessed the eligibility of the studies for inclusion and extracted the data. All authors contributed to the analysis and to writing the manuscript and agreed on the final draft.

Declarations of interest

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